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Oxidation of Azides by the HOF·CH_3CN: A Novel Synthesis of Nitro Compounds

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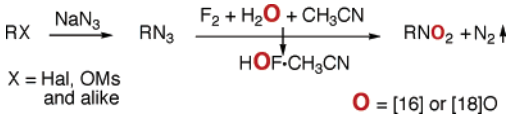

The HOF·CH_3CN complex, readily prepared by passing F_2 through aqueous acetonitrile, is an exceptionally efficient oxygen transfer agent. It is unique in its capacity to oxidize various azides into the corresponding nitro derivatives. This method requires short reactions times and room temperature or below, and the desired nitro compounds were usually isolated in very good yields. The respective nitroso derivatives are believed to be the intermediates in this reaction. Functional groups such as aromatic rings, ketones, nitriles, halides, alcohols, and esters are tolerated. Sulfides react with HOF·CH_3CN usually at the same rate as azides. Amines and olefins, however, react faster, so they have to be protected first. Nitro derivatives with various oxygen isotopes can be made using the labeled $H^{18}OF\cdot CH_3CN$. In the case of chiral azides the stereochemistry around the nitrogen-bonded carbons is retained.

Introduction

Nitro compounds constitute an important class of materials in organic chemistry. In many cases they are key synthetic intermediates, whereas in others they are the final products useful in the preparation of explosives, dyes, plastics, perfumes, pharmaceutics[1] and more. They have also an important role in evaluating many mechanistic concepts.[2]

Nitro compounds are usually obtained either through a direct nitration of hydrocarbons under harsh conditions or through a nitration of anionic intermediates originating from alkyl halides, alkenes or ketones (α-nitration).[1,2] For such transformations, a variety of nitrating agents (electrophilic, radical, and nucleophilic) have been used. Corey developed a multistep method of converting azides first to phosphine imines ($RN_3 \rightarrow RN{=}PR_3$), which had to be isolated and then oxidized by ozone. The nitro derivatives thus obtained (40−70% yield) were accompanied by the corresponding phosphine oxides as well as by aldehydes, which in certain cases were the sole products.[3] A direct and high yield transformation of azides to nitro derivatives, however, appeared only in the wish list of those dealing with nitro and azide chemistry.[4,5]

About 20 years ago we introduced the HOF·CH_3CN complex[6] and from that time its excellent oxygen transfer abilities have become very clear. It is readily prepared by bubbling nitrogen-diluted fluorine through aqueous acetonitrile and is used for the epoxidation of any type of olefins[7] and the oxidation of alcohols[8] and methyl ethers[9] to ketones, and these in their turn could be transformed to esters via Bayer−Villiger reaction.[8] This reagent was also used to transfer oxygen atoms to sulfides, including electron-depleted ones,[10] thiophenes[11] and polythiophenes,[12] converting all of them to the corresponding *S*,*S*-dioxo derivatives. Reactions with primary amines resulted in nitro compounds,[13] whereas tertiary ones produced the corresponding *N*-oxides,[14] including 1,10-*N*,*N*′-phenanthroline dioxides derivatives that had eluded chemists for so many decades.[15] These

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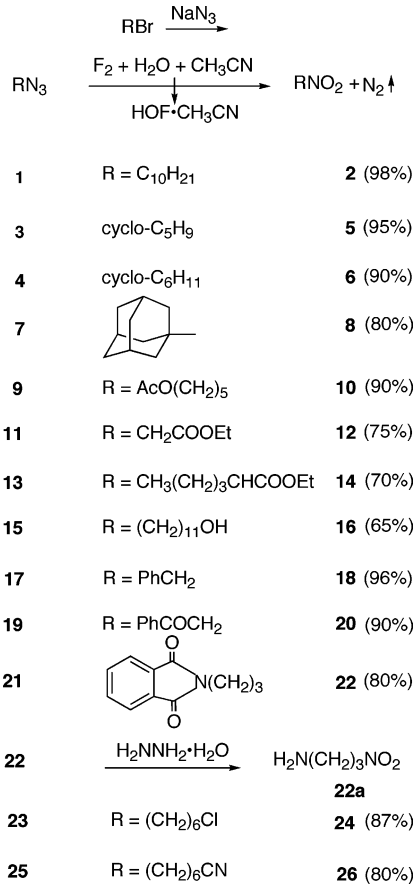
SCHEME 1. Direct Oxidation of Azides to Nitro Compounds



reactions and many more[16] are evidence of the high synthetic potential of HOF·CH_3CN.

We report here of a new and unprecedented direct oxidation of azides, easily obtained from alkyl halides or alcohol derivatives, to the corresponding nitro compounds by the HOF·CH_3CN complex.[5]

Results and Discussion

1-Azidodecane (**1**) was readily prepared from bromodecane and sodium azide in excellent yields following a literature procedure.[17] A solution of 3 molar equiv of HOF·CH_3CN (each molar equivalent is a supplier of one oxygen atom) was added to a methylene chloride solution of **1** at 0 °C. A release of N_2 was observed, and in a few seconds the reaction was over, forming 1-nitrodecane (**2**)[18] in 98% yield (Scheme 1).

Secondary azides also reacted well. Cyclopentyl (**3**) and cyclohexyl (**4**) azides, prepared from the corresponding bromides,[17] needed only 5 s at 0 °C in order to be converted to nitrocyclopentane (**5**) and nitrocyclohexane (**6**) in good yields. The same is true for tertiary azides such as 1-azidoadamantane (**7**), which was transformed to 1-nitroadamantane (**8**)[19] in 95% yield. Ester groups do not pose any problems either, as evident from the reaction of 5-azidopentyl acetate (**9**), resulting in 5-nitropentyl acetate (**10**)[20] in 90% yield.

The family of α-nitro acids is quite useful as a starting point for various reactions, and several synthetic methods have been devised for the preparation of its members. Save the oxidation of amino acids by HOF·CH_3CN,[21] most methods are based on a combination of two fragments such as nitroacetate and an alkyl group or carboxylic acid derivatives and a nitro compound.[22] These procedures are usually characterized by long reaction times and low yields. Direct conversion of α-azido esters to the corresponding nitro derivatives can serve as an alternative efficient method for preparing these compounds. Thus, reacting ethyl azidoacetate (**11**) with 6 equiv of HOF·CH_3CN at 0 °C produced ethyl nitroacetate[21] (**12**) in a few minutes reaction. Ethyl 2-azido hexanoate (**13**) behaved similarly, forming ethyl 2-nitrohexanoate (**14**) in good yield.

Despite the fact that the HOF·CH_3CN complex is able to oxidize primary alcohols,[8] the short reaction times with the azido group enabled its selective oxidation without affecting such an hydroxyl group. 11-Azidoundecanol (**15**) could serve as an example by its conversion to the corresponding 11-nitroundecanol (**16**)[23] in a few seconds using 3 equiv of HOF·CH_3CN complex. Although HOF·CH_3CN is known to react slowly with aromatics,[24] the ring in benzyl azide (**17**) does not interfere with the fast reaction of the azido moiety, forming almost quantitatively α-nitrotoluene (**18**). Similarly, reacting α-azido acetophenone (**19**) with 3 molar equiv of HOF·CH_3CN produced α-nitro acetophenone (**20**) in a clean, few seconds reaction. The same is true for *N*-(3-azidopropyl)phthalimide (**21**), which was reacted with 4 equiv of the HOF·CH_3CN complex to form *N*-(3-nitropropyl)phthalimide[25] (**22**) in 80% yield. Cleavage of the phthalimide group with hydrazine hydrate produced 1-amino-3-nitropropane (**22a**),[26] a member of the difficult to obtain nitro amino derivatives.

Reacting 1-azido-6-chlorohexane (**23**) with 3 equiv of HOF·CH_3CN for a few seconds produced the corresponding new nitro derivative (**24**) in 87% yield. An alternative method for the preparation of similar compounds uses direct chlorination of the nitro derivative, but this option requires harsh conditions and results in low yields.[27] Nitriles are also tolerated, and treating 1-azido-6-cyanohexane (**25**) with 3 equiv of HOF·CH_3CN forms 1-cyano-6-nitrohexane (**26**) in a few seconds without affecting the cyano group.

Unlike the very short reaction times required by the aliphatic azides, it took almost 1 h for 10 equiv of HOF·CH_3CN to react with azidobenzene (**27**) at room temperature to form nitroben-

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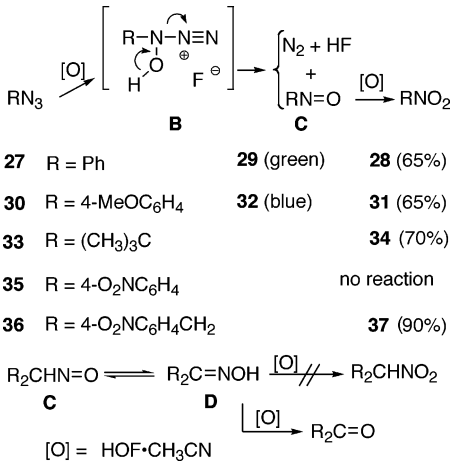
SCHEME 2. Proposed Mechanism for Direct Oxidation of Azides to Corresponding Nitro Derivatives

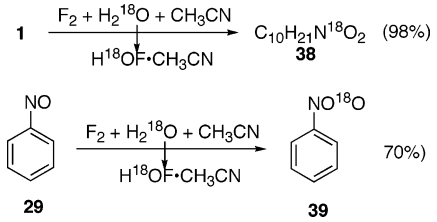


zene (**28**) in 65% yield (Scheme 2). Nitrosobenzene (**29**) on the other hand was quantitatively oxidized at 0 °C with 1 equiv of HOF·CH$_3$CN in a matter of seconds forming the same **28**. 4-Methoxyazidobenzene (**30**) whose carbon bonded nitrogen is more electron rich than the parallel nitrogen in **27**, reacted considerably faster (10 min. versus 1 h) at 0 °C, to give 4-nitroanisole **(31)** in 65% yield. What is more, an intensive blue color of the nitroso derivative (**32**) appeared, for a few seconds and then faded away. The usually colored nitroso species were not observed in the aliphatic series apparently because the oxidation step from a nitroso to a nitro derivative is too fast. Even the sterically hindered *t*-BuN$_3$ (**33**) reacted so fast at −78 °C to produce *t*-BuNO$_2$ (**34**) that we were unable to notice any blue coloration characteristic to the molecule of *t*-BuNO. Unlike all other examples 4-azidonitrobenzene (**35**) was unreactive toward the electrophilic oxygen of the reagent because of the low basicity of the carbon bonded azido nitrogen. Introducing a methylene spacer between the deactivated aromatic ring and the azido group as in 4-nitrobenzyl azide (**36**) enabled the formation of (4-nitrobenzene)-nitromethane (**37**) in a few minutes and in 90% yield. These observations support a two steps reaction mechanism: the first and the slower is an attack on the relatively electron rich nitrogen by the reagent's electrophilic oxygen forming intermediate **B**, that immediately decomposes to the corresponding nitroso derivative (**C**), HF and N_2. Consequently, the respective nitroso derivative reacts fast with an additional molecule of HOF·CH$_3$CN forming eventually the desired nitro compound (Scheme 2).

An alternative explanation for aliphatic azides bearing an α hydrogen atom could be brought up since the nitroso derivatives could rearranged to oximes **D**,[28] followed by further oxidation to the target nitro compound.[29] Independent experiments, however, showed that when ketoximes, as well as other C=N derivatives, were reacted with HOF·CH$_3$CN they resulted in quantitative formation of the starting carbonyl derivatives.[30]

One of the advantages of HOF·CH$_3$CN is that its electrophilic oxygen originates from water, which is the best source for all oxygen isotopes. We have passed fluorine through a solution of acetonitrile and $H_2{}^{18}O$ and obtained H^{18}OF·CH$_3$CN, which

SCHEME 3. Incorporation of One or Two ^{18}O Isotopes into the Nitro Moiety



was reacted with **1** (Scheme 3). HRMS (CI) *m*/*z* = 190.157446, calcd. for $C_{10}H_{20}N^{18}O_2$ (M-1) 190.157894, confirmed that the two oxygen atoms of the [18]O-nitrodecane (**38**, 98% yield) are indeed the expected heavy oxygen isotopes. Another experiment along this line was reacting nitrosobenzene (**29**) with 1 equiv of H^{18}OF·CH$_3$CN. The HRMS (CI) of the nitrobenzene (**39**), which was formed after a few seconds, *m*/*z* = calcd 125.036273, found 125.036477 $(M)^+$, clearly indicated that only one ^{18}O atom was incorporated without any scrambling of the oxygen atoms under the reaction conditions. This increases the probability that the reaction proceeds through the intermediacy of the nitroso moiety (Scheme 3).

The speed of the reaction made us wonder if other oxygen transfer agents would be as effective as HOF·CH$_3$CN. We refluxed methylene chloride solutions of **1** with 8 molar equiv of MCPBA for 6 h and recovered more than 98% of the starting material. Same results were obtained after treating **1** with 14 molar equiv of dimethyldioxirane (DMDO) for several hours. It seems that HOF·CH$_3$CN is indeed a stand-alone oxygen transfer agent when the transformation of azides to nitro compounds is considered.

As we have seen above, HOF·CH$_3$CN reacts faster with the azido moiety than with primary alcohols, aromatic rings, aliphatic halides, ketones, and esters. To further evaluate the scope of this method, we reacted compounds that contain the azide moiety along with some other more competitive functional groups such as a sulfide, olefin, amine, and the like (Scheme 4).

In the past, sulfides had been oxidized to sulfones in excellent yields using HOF·CH$_3$CN complex.[9] Azidomethyl phenylsulfide (**40**) was reacted with 1 molar equiv of HOF·CH$_3$CN, producing a mixture arising from attacks on both the nitrogen and the sulfur atoms. Adding a total of 4 molar equiv of the oxidation agent, however, produced nitromethyl phenyl sulfone (**41**) in 90% yield. We have also examined 10-azido-1-decene (**42**). Applying 0.8 equiv of HOF·CH$_3$CN for a short time left the azido group untouched, while the double bond was epoxidized, forming 10-azido-1,2-epoxy decane (**43**). Adding 3.5 equiv of the oxidizing agent enabled a fast reaction on both the azido group and the double bond, forming 1,2-epoxynitrodecane (**44**) in 85% yield.

Amines are also known to react fast with HOF·CH$_3$CN,[13] and similarly to the above examples they proved to react faster than the azido group. Reacting 1-amine-11-azido-3,6,9-trioxaundecane (**45**) with 2 molar equiv of HOF·CH$_3$CN produced 1-azido-11-nitro-3,6,9-trioxaundecane (**46**) in 65% yield. An attempt to slow the reaction on the amine group by using its hydrochloride did not change the outcome apparently because of a not negligible equilibrium between the salt and the free amine in the polar media. However, protecting it as a trifluoroacetate (**47**) enabled us to selectively oxidize the azido group, and the amino-nitro derivative **48** was obtained in 75% yield (Scheme 4).

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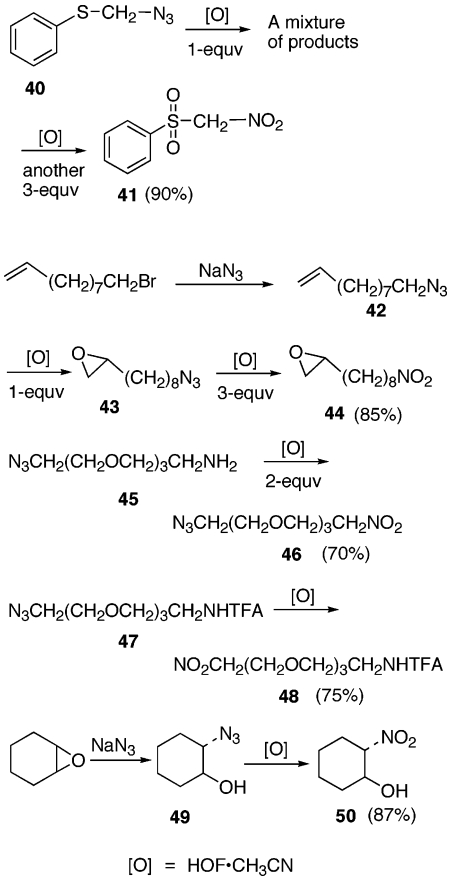
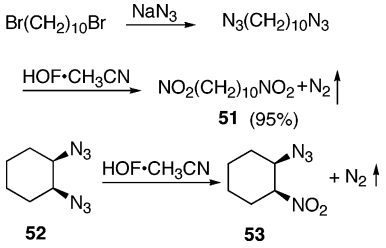
SCHEME 4. Compatability with Other Functional Groups



SCHEME 5. Preparation of Dinitro Derivatives

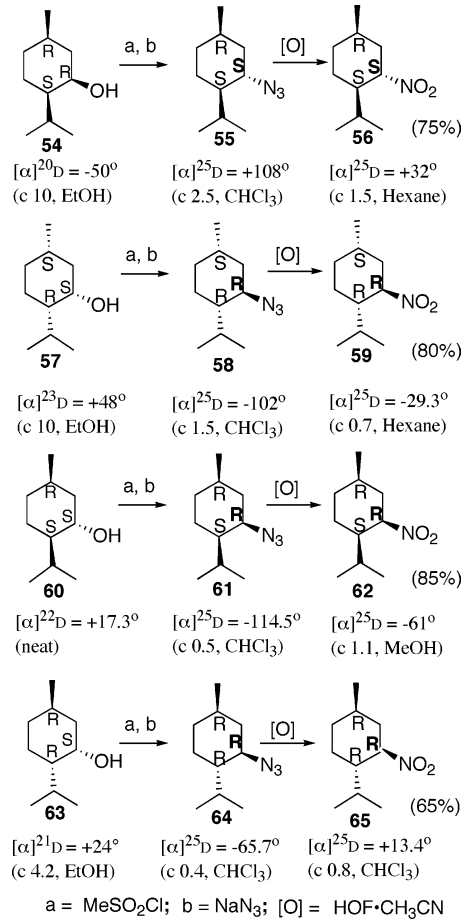


The priorities were reversed with secondary alcohols, which are easily transformed to ketones when they are the sole functional group in a molecule.[8] When the azido group was also present, the latter reacted faster as observed with 2-azido cyclohexanol (**49**), which required 3 equiv of HOF•CH_3CN to produce 2-nitrocyclohexanol (**50**) in 87% yield.

Another useful application of this method was the formation of dinitro compounds, which could be obtained from the respective dihalo derivatives. The high yield and fast formation of 1,10-dinitrodecane (**51**) from 1,10-diazidodecane is illustrative (Scheme 5). Such polynitro compounds have found many uses in organic syntheses.

Vicinal diazo compounds such as *cis*-1,2-diazidocyclohexane **52** could not be transferred to their dinitro analogues by the present reaction. Attempts to react **52** with more than 15 equiv of HOF•CH_3CN resulted in the oxidation of only one of the azido groups to the corresponding 1-azido-2-nitrocyclohexane (**53**) in 65% yield. The reason for this partial oxygen transfer lies in the fact that this is a stepwise reaction. Once one nitro group is formed the basicity of the remaining carbon-bonded

SCHEME 6. Oxidation of Chiral Azides using HOF•CH_3CN



azido nitrogen is reduced to such an extend that the electrophilic oxygen of the reagent can no longer attach itself to it.

Transferring the azido group to the nitro one does not affect the stereochemistry around the nitrogen-bonded carbon. We have reacted four optically active menthol derivatives, substituting their hydroxyl group via the respective mesylates by the azide moiety through a classical S_N2 reaction. These compounds were then reacted with HOF•CH_3CN, and in all cases no racemization was observed.

Thus, the enantiomeric (1*S*,2*S*,5*R*)-(−)-azidomenthane (**55**)[31] and (1*R*,2*R*,5*S*)-(+)-azidomenthane (**58**) were prepared from the (1*R*,2*S*,5*R*)-(−)-menthol (**54**) and (1*S*,2*R*,5*S*)-(+)-menthol (**57**) (Scheme 6). Both **55** and **58** proved to be somewhat difficult to oxidize to the corresponding nitro derivatives **56**[32] and the unknown **59**. This resistance was overcame by using 30 equiv of the oxidative agent during 2 h of reaction. The reason for such relatively unusual conditions is the bulky isopropyl group, which has a very strong influence on the reaction center. On the other hand, the carbon-bonded nitrogen in the isomeric (1*R*,2*S*,5*R*)-(+)-azidomenthane **61** and (1*R*,2*R*,5*R*)-(+)-azidomenthane **64**, made from the corresponding (1*S*,2*S*,5*R*)-(+)-neomenthol (**60**) and (1*S*,2*R*,5*R*)-(+)-isomenthol (**63**), is much less affected by the steric hindrance of the isopropyl, and the oxidation process leading to **62**[29] and to the unknown **65** requires only 6 equiv of the oxidation agent and about 30 min of reaction

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time. In all cases no considerable racemization was observed as evident from the optical rotation of all products.

Conclusion

The oxidation with HOF·CH_3CN described above is the first direct conversion of azides to nitro derivatives in very good yields without affecting the stereochemistry around the C−N bond. We hope that this new method will become one of the standard procedures for the preparation of nitro compounds. Considering the commercial availability of premixed fluorine/nitrogen mixtures and the technical ease of the reaction, chemists should be encouraged to take advantage of the unique synthetic value of HOF·CH_3CN complex as a convenient reagent in organic syntheses. We believe that time has arrived that the prejudice against fluorine, especially from various "safety committees" in some organizations, should be reconsidered.

Experimental Section

General Procedure for Working with Fluorine. Fluorine is a strong oxidant and very corrosive material. It should be used only with an appropriate vacuum line.[14a] For the occasional user, however, various premixed mixtures of F_2 in inert gases are commercially available, simplifying the process. If elementary precautions are taken, work with fluorine is relatively simple, and we have had no bad experience working with it.

General Procedure for Producing HOF·CH_3CN. Mixtures of 10−20% F_2 in nitrogen were used in this work. The gas mixture was prepared in a secondary container prior to the reaction and passed at a rate of about 400 mL per minute through a cold (−15 °C) mixture of 100 mL of CH_3CN and 10 mL of H_2O. The development of the oxidizing power was monitored by reacting aliquots with an acidic aqueous solution of KI. The liberated iodine was then titrated with thiosulfate. Typical concentrations of the oxidizing reagent were around 0.4−0.6 mol/L.

General Procedure for Reacting Azides with HOF·CH_3CN. An appropriate amount of azide (usually 0.4−0.6 g) was dissolved in about 30 mL of $CHCl_3$, and the mixture was cooled to 0 °C. The oxidizing agent was then added in one portion to the reaction vessel. The excess of HOF·CH_3CN was quenched with saturated sodium bicarbonate and extracted with $CHCl_3$, the organic layer was dried over $MgSO_4$, and the solvent was evaporated. The crude product was usually purified by vacuum flash chromatography using Silica gel 60-H (Merck). The spectral and physical properties of the known products thus obtained were compared either with those of authentic samples or with the properties reported in the literature. In every case an excellent agreement was obtained. All known compounds, with the exception of the commercial products, were referenced throughout this work. Data for the new compounds or for those not well defined in the literature are given below and in Supporting Information.

1-Chloro-6-nitro-hexane (**24**) was prepared from **23** (0.5 gr, 3.1 mmols) as describe above, resulting in a 87% yield of a yellow liquid: ^{1}H NMR 4.4 (2 H, t, J = 3.4 Hz), 3.54 (2 H, t, J = 3.2 Hz), 2.03 (2 H, quin, J = 3.6 Hz), 1.79 (2 H, quin, J = 3.3 Hz), 1.38−1.54 ppm (4H, m). ^{13}C NMR 27.5, 28, 29.1, 34, 46.6, 77.4 ppm. MS (CI) m/z = 166.1 $(M + 1)^+$. Anal. Calcd for $C_6H_{12}ClNO_2$: C, 43.51; H, 7.30; N, 8.46. Found: C,43.80; H,7.28; N,8.32.

Acknowledgment. This work was supported by the Israel Science Foundation.

Supporting Information Available: Syntheses of compounds **26**, **44**, **48**, **53**, **59**, and **65** and copies of ^{1}H and ^{13}C NMR for compounds **56** and **59**. This material is available free of charge via the Internet at http://pubs.acs.org.

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